

# Dementia with Lewy bodies

## *Review of diagnosis and pharmacologic management*

Christopher Frank, MD, CCFP

### ABSTRACT

**OBJECTIVE** To review clinical features of dementia with Lewy bodies (DLB) and to guide family physicians in pharmacologic management, including medications to avoid.

**QUALITY OF EVIDENCE** A MEDLINE search of literature from 1995 to 2002 used the MeSH terms dementia with Lewy bodies/diagnosis, dementia with Lewy bodies/therapy, and antipsychotics/dementia with Lewy bodies. Level II and III evidence was available for diagnosis and treatment of DLB. One randomized controlled trial of rivastigmine was reviewed and appraised.

**MAIN MESSAGE** Dementia with Lewy bodies is common. Diagnosis can be made by family physicians using clinical criteria including presence of dementia with marked fluctuation in performance, hallucinations, and the onset of parkinsonism. Cholinesterase inhibitors should be considered for neuropsychiatric symptoms. Levodopa-carbidopa combinations should be considered for treatment of parkinsonism. Neuroleptics should be used with caution because of the risk of serious sensitivity reactions. If they are needed, atypical agents could be safer.

**CONCLUSION** Recognition and diagnosis of DLB is important to optimize pharmacologic management and to minimize risk of adverse reactions to neuroleptics.

### RÉSUMÉ

**OBJECTIF** Rappeler les principales caractéristiques cliniques de la démence à corps de Lewy (DCL) et aider le médecin de famille à choisir la médication appropriée et à éviter celle qui ne l'est pas.

**QUALITÉ DES PREUVES** On a utilisé les termes MeSH «*dementia with Lewy bodies/diagnosis*», «*dementia with Lewy bodies/therapy*» et «*antipsychotics/dementia with Lewy bodies*» pour consulter MEDLINE entre 1995 et 2002. Cette recherche a fourni des preuves de niveaux II et III à propos du diagnostic et du traitement. Un essai randomisé portant sur la rivastigmine a fait l'objet d'une attention et d'une évaluation particulières.

**PRINCIPAL MESSAGE** La DCL est une affection fréquente. Le médecin de famille peut en faire le diagnostic à partir de critères cliniques incluant une démence associée à d'importantes fluctuations de performance, des hallucinations et l'apparition d'un Parkinson. On suggère d'utiliser des inhibiteurs de la cholinestérase pour les symptômes neuro-psychiatriques et une combinaison levodopa-carbidopa pour le parkinsonisme. Les neuroleptiques doivent être utilisés avec prudence à cause du risque de sévères réactions d'hypersensibilité. Dans les cas où ils doivent être prescrits, les agents atypiques pourraient s'avérer plus sécuritaires.

**CONCLUSION** Il importe de reconnaître et de diagnostiquer la DCL afin d'optimiser le traitement pharmacologique et de minimiser les risques de réactions indésirables aux neuroleptiques.

*This article has been peer reviewed.*

*Cet article a fait l'objet d'une évaluation externe.*

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**D**ementia is a common problem encountered by family physicians. Approximately 10% of people older than 65 years have dementia; this number increases to more than 40% among those older than 80.<sup>1</sup>

Dementia with Lewy bodies (DLB) is thought to account for up to 20% of cases of dementia. Although there remains some controversy about where DLB fits into the taxonomy of neurologic illness, it is important for family physicians to include it in the differential diagnosis of the causes of dementia. Recognition and diagnosis can prevent some of the serious consequences of this condition and allow for pharmacologic therapy. This paper summarizes the clinical diagnosis of DLB and reviews the evidence for drug therapy.

### Quality of evidence

MEDLINE was searched from 1995 to 2002, using the MeSH terms dementia with Lewy bodies/diagnosis, dementia with Lewy bodies/therapy, Lewy bodies/drug therapy, and antipsychotics/dementia with Lewy bodies. References cited in review articles were identified and used when appropriate. All original research articles and case studies were included (32 about diagnosis, nine about cholinesterase inhibitors, five about neuroleptics). Review articles and studies of genetic and pathologic diagnosis were not included. Given the limited number of randomized controlled trials (RCTs), articles were not excluded on the basis of methodology. The DLB consortium consensus guidelines<sup>2,3</sup> were used.

Almost all the original research articles on treatment were retrospective studies, prospective uncontrolled trials, or case reports or case series. One RCT studied the use of rivastigmine.

### Background

Dementia with Lewy bodies was first described in 1961 and was viewed as a rare form of dementia. As a disorder in the spectrum between Parkinson disease (PD) and Alzheimer disease (AD), it has been referred to in the past using terms such as Parkinson's disease plus Alzheimer's. Pathologic series and hospital-based autopsy series suggest prevalence ranging from 10% to 20% of late-onset dementias.<sup>2</sup> Clinical studies tend to suggest lower prevalence rates; a recent community survey in London estimated a prevalence of 10.9%.<sup>4</sup>

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**Dr Frank** is an Assistant Professor in the Department of Medicine at Queen's University in Kingston, Ont.

Lewy bodies are classically associated with PD. They are rarely seen in the cerebral cortex in PD but are in several areas of the cortex (temporal, frontal, parietal) in DLB. In addition, 75% to 90% of patients also have some neuropathologic features of AD (senile plaques, low burden of neurofibrillary tangles). Consensus guidelines for pathologic diagnosis of DLB were published along with the clinical guidelines.

Dementia with Lewy bodies usually presents in later life, with a mean age of onset between 75 and 80 years. There is a slight male predominance, unlike AD. Although the progression and prognosis of DLB have traditionally been viewed as worse than those of AD, studies using prospective methods have not found any difference between AD and DLB in survival, age of onset, or age at death.<sup>5,6</sup>

### Clinical presentation and diagnosis

Consensus guidelines for diagnosis of DLB were published in 1996<sup>2</sup> and reviewed in 1999.<sup>3</sup> Clinical criteria are summarized in **Table 1**<sup>2,7,8</sup> (level II and III evidence).

**Table 1. Clinical criteria for dementia with Lewy bodies**

#### CENTRAL FEATURE OF DEMENTIA

Progressive decline of cognitive function of sufficient magnitude to impair normal social or occupational function

#### CORE FEATURES OF DEMENTIA (MUST HAVE TWO FOR PROBABLE DLB, MUST HAVE ONE FOR POSSIBLE DLB)

Fluctuation in cognition with pronounced variations in alertness and attention

Recurrent visual hallucinations

Motor parkinsonism

#### FEATURES SUPPORTIVE OF DLB DIAGNOSIS

Repeated falls

Syncope

Transient loss of consciousness

Neuroleptic sensitivity

Systematized delusions

Hallucinations in other sensory modalities

REM sleep behaviour disorder

*DLB—dementia with Lewy bodies, REM—rapid eye movement.*

*Data from McKeith et al,<sup>2</sup> Del Ser et al,<sup>7</sup> and Boeve et al.<sup>8</sup>*

Presence of dementia is necessary for the diagnosis of DLB. Cognitive changes are distinct from the dementia of AD and PD. Memory loss is not always a prominent early feature; deficits can be in

memory retrieval, as they are in PD.<sup>9</sup> Other cognitive features distinguishing DLB from AD are a greater prominence of attention, executive task function, and visuospatial problems.<sup>9,10</sup> Difficulty with changing mental set, perseveration, and intrusion are more likely with DLB than with AD.<sup>11</sup> Given the differences seen with DLB, clinicians should emphasize the attention, constructional (worse in DLB), and memory (better in DLB) subscores when using the Mini-Mental State Examination.<sup>12</sup> Performance on a clock drawing test can highlight executive task and visuospatial problems.<sup>13</sup> Other psychopathology seen early in DLB includes depression, anxiety, apathy, and anhedonia.<sup>14,15</sup>

**Fluctuation in cognitive performance.** A core feature of this type of dementia is the fluctuation in cognitive performance, which can occur early in the illness. Fluctuations in performance are likely related to marked variation in attention and alertness. There is no typical pattern or consistent diurnal variation in attention. Attention and concentration can vary over hours to days to weeks for the same person. Patients sometimes improve greatly but transiently with novelty and environmental stimulation. Caregivers often describe decreased awareness of surroundings with periods of "blankness" lasting for minutes. The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale are tools that can be used in the office to assess this core feature.<sup>16,17</sup>

**Visual hallucinations.** The second core feature for family physicians to be aware of is development of visual hallucinations. Hallucinations are the major psychotic feature distinguishing DLB from AD. In DLB, hallucinations are typically recurrent, are well formed, and are usually detailed. Common themes are of animals and people intruding into the patient's home, and images might or might not be frightening to patients. Patients could have a degree of insight into the unreality of the perceptual changes, but delusions can result from hallucinations. Such conditions as visual loss and decreased level of consciousness can exacerbate visual hallucinations. Auditory, olfactory, and tactile hallucinations occur less frequently.<sup>2</sup> Presence of hallucinations with substantial fluctuation in attention can lead clinicians to diagnose delirium. Indeed, DLB should be considered in the differential diagnosis of recurrent or "chronic" delirium.

The decision to treat visual hallucinations in DLB must depend on patients' response to hallucinations and any effect on function and quality of life. Some

patients with DLB have marked neuroleptic sensitivity. In some cases, serious adverse reaction to neuroleptics is the initial clue to the presence of underlying DLB.

**Motor parkinsonism.** The final core feature of DLB is the presence of motor parkinsonism. This feature varies in severity, and patients usually have rigidity and bradykinesia, gait changes, and masklike faces.<sup>18</sup> Resting tremor is less common in DLB than in PD. Development of dementia within 12 months of extrapyramidal signs suggests DLB, whereas late development of dementia makes PD with Parkinson's dementia more likely.<sup>2</sup> Parkinsonism is also occasionally seen in advanced AD and some other dementias, sometimes secondary to neuroleptic use by patients with dementia.

As noted above, more than 50% of DLB patients have marked sensitivity to neuroleptics. This sensitivity can include rapid and irreversible worsening of parkinsonism, and occasionally involves a neuroleptic malignant syndrome-like presentation with autonomic instability. Neuroleptics can accentuate the attention problems and fluctuation in cognition, sometimes causing marked somnolence. There is a threefold increase in mortality related to neuroleptic use, mostly secondary to marked functional decline.<sup>2</sup>

Other features support the diagnosis of DLB (**Table 1**<sup>2,7,8</sup>). Falls are not necessarily directly related to the severity of parkinsonism.<sup>19,20</sup> Syncopal attacks with complete loss of muscle tone could be due to involvement of the brainstem and autonomic nervous system. Transient loss of consciousness without loss of muscle tone could represent severely fluctuating level of alertness.<sup>2</sup> Other diagnoses to consider are shown in **Table 2**.

Accuracy of guidelines for clinical diagnosis has been studied. Retrospective chart reviews reported sensitivities from 0.22 to 0.75 with better specificity (0.79 to 1.0).<sup>21-24</sup> A prospective study (n=29) used the criteria for diagnosis and performed autopsies on patients to evaluate the clinical diagnosis. The sensitivity and specificity of criteria were 0.83 and 0.95, respectively.<sup>25</sup> These findings suggest that patients fulfilling the criteria are likely to have DLB, but that the criteria do not identify some patients with the disease, particularly those with mild disease or with concurrent AD.<sup>26</sup>

The role of neuroimaging remains unclear<sup>27-32</sup> (level II evidence). Structural imaging with computed tomography and magnetic resonance imaging can show generalized atrophy, but atrophy tends to correlate more with severity than with type of dementia.<sup>31</sup>

Volumetric measurements of temporal lobes suggest a different pattern of loss in AD than in DLB, but clinical applications are uncertain.<sup>27,29,33</sup> Comparisons of electroencephalographs among patients with AD and DLB have been inconclusive.<sup>34</sup> Occipital and posterior association cortex hypoperfusion on single photon emission computed tomography (SPECT) scanning have been reported as more prominent, but the clinical role of functional brain scanning is unclear.<sup>35-37</sup>

**Table 2. Differential diagnosis of patients with dementia with Lewy bodies**

**OTHER DEMENTIAS**

Alzheimer disease  
Frontotemporal dementias  
Vascular dementia

**OTHER NEUROLOGIC ILLNESSES**

Idiopathic Parkinson disease  
Multisystem atrophy  
Supranuclear palsy  
Creutzfeldt-Jakob disease

**OTHER PSYCHIATRIC ILLNESSES**

Mania  
Psychotic depression  
Late-onset delusional disorder

**CAUSES OF DELIRIUM**

Infection  
Metabolic and endocrine causes  
Medications  
Stroke and vascular causes  
Withdrawal (medication and alcohol)

**Treatment**

As with other dementias, nonpharmacologic treatment of DLB is a crucial aspect of primary care management. Education is important to help patients and families understand and deal with specific symptoms, such as hallucinations and cognitive fluctuations, as well as with the general issues of caring for a person with dementia. Educating families and patients can also reduce inappropriate use of neuroleptics, particularly in new settings (such as after admission to hospital or to a nursing home).

**Treatment of dementia in DLB.** Basic science research suggests that patients with DLB have a greater cholinergic deficit than those with AD,<sup>38</sup> prompting several studies on the use of cholinesterase inhibitors for

Lewy bodies.<sup>39</sup> One RCT examined the use of rivastigmine in DLB, and several case reports, series, and open-label studies have been published (Table 3).<sup>40-47</sup>

Wesnes and associates<sup>40</sup> and McKeith et al<sup>41,46</sup> reported a well designed study of 120 patients with DLB using rivastigmine for 20 weeks versus a placebo. Patients taking rivastigmine had less apathy and anxiety, and fewer hallucinations and delusions, than those taking placebo. Results on computerized tests of cognition, especially tasks involving attention, improved with treatment. Improvements seen with rivastigmine returned to baseline after discontinuation. As in other trials of rivastigmine, nausea and vomiting were the most common side effects, but no worsening of parkinsonism was noted. The study was limited by a high drop-out rate, and intention-to-treat analysis did not show a statistically significant change for core neuropsychiatric symptoms. An increase in the percentage of patients showing improvement of at least 30% from baseline (47.5% versus 27.9% of placebo subjects), however, was significant.

Cholinesterase inhibitors are not approved for treatment of DLB in Canada, but preliminary evidence suggests that they have an important role (level II and III evidence). They might improve neuropsychiatric symptoms and reduce the need for potentially harmful neuroleptic drugs.<sup>48</sup> Evidence from more RCTs will likely be available within the next few years.

**Treatment of parkinsonism.** The degree of parkinsonism found in patients with DLB varies, and the need for anti-Parkinson's medications is inconsistent. Treatment with levodopa-carbidopa combinations should be considered when symptoms impair function. Most of the evidence for benefit comes from case series<sup>49,50</sup> (level II evidence). Response to levodopa does not appear to be consistent but is common, and no significant increase in common levodopa side effects, such as hallucinations, is reported.

**Treatment of psychotic features.** Despite concerns about neuroleptic sensitivity, evidence of the "best" neuroleptic to treat psychotic symptoms of DLB is limited (level II evidence). Case reports of sensitivity reactions among DLB patients taking risperidone<sup>51</sup> are balanced by reports of therapeutic benefit from risperidone.<sup>52</sup> A retrospective study of quetiapine (mean dose 69 mg/d) use in PD and DLB patients found worsening of motor symptoms in 32% of PD and 27% of DLB patients, but no sensitivity reactions were noted.<sup>53</sup> In a prospective series of

**Table 3. Studies using cholinesterase inhibitors**

STUDY	SAMPLE	DESIGN	RESULTS
Efficacy of rivastigmine in DLB: an RCT international study <sup>46</sup>	120	Placebo-controlled, double-blind RCT for 20 wk done in 3 countries with rivastigmine (6-12 mg/d)	<ul style="list-style-type: none"> <li>• High drop-out rate in treatment group</li> <li>• Patients receiving treatment had significantly less apathy and anxiety and fewer delusions and hallucinations (only a non-significant trend with ITT analysis)</li> <li>• 47.5% of treatment group had 30% improvement versus 27.9% of placebo on ITT analysis</li> <li>• Differences between placebo and drug tended to disappear after discontinuation of treatment</li> </ul>
Effects of rivastigmine on cognitive function in DLB: an RCT using the cognitive computerized assessment system <sup>40</sup>	120	Placebo-controlled, double-blind RCT for 20 wk with rivastigmine, reports results with computerized assessment system	<ul style="list-style-type: none"> <li>• Statistically significant improvement in attention and overall quality of memory score with ITT analysis</li> <li>• Decline to baseline 3 wk after stopping treatment</li> </ul>
Rivastigmine in DLB: preliminary findings from an open trial <sup>41</sup>	11 with DLB, subgroup of above sample	Open-label study with rivastigmine (3-12 mg)	<ul style="list-style-type: none"> <li>• After 12 wk, improved NPI scores for delusions, apathy, agitation, and small decrease in hallucinations</li> <li>• Parkinsonism tended to improve</li> </ul>
Long-term use of rivastigmine in DLB: an open-label trial <sup>43</sup>	29	Open-label study with rivastigmine for up to 96 wk	<ul style="list-style-type: none"> <li>• Improvement in MMSE score (NPI) at 24 wk</li> <li>• By 96 wk, neither MMSE nor NPI significantly worse than at baseline</li> </ul>
Rivastigmine in DLB: effects on cognition, neuropsychiatric symptoms, and sleep <sup>42</sup>	8	Case series with rivastigmine	<ul style="list-style-type: none"> <li>• 7 of 8 patients had improved MMSE and NPI scores</li> <li>• Sleep disruption improved in 6 of 7</li> <li>• 1 patient had no improvement</li> </ul>
Better cognitive and psychopathologic response to donepezil in patients prospectively diagnosed with DLB <sup>44</sup>	4 with DLB 12 with AD	Single-blind trial comparing DLB patients with AD patients using donepezil (5 mg)	Improved MMSE score and improved caregiver reports of psychopathologic state at 6 mo among the few DLB subjects
Donepezil for treatment of DLB: case series of 9 patients <sup>47</sup>	9 with DLB	Case series with 5-10 mg of donepezil for 12 wk	<ul style="list-style-type: none"> <li>• Improvement in MMSE score (mean change 4.4)</li> <li>• Improvement in hallucinations among 8 subjects</li> <li>• In 3 patients, parkinsonism worsened</li> </ul>
Acetylcholinesterase inhibition in DLB: results of a prospective pilot trial <sup>45</sup>	6 with DLB and 6 with AD	Open, non-randomized intervention trial using tacrine (80 mg/d)	<ul style="list-style-type: none"> <li>• Variable response to treatment in DLB group</li> <li>• No significant difference seen in response of whole DLB group compared with AD group</li> <li>• DLB patients who responded had improved Dementia Rating Scale memory subscores</li> <li>• Progression of parkinsonism noted in all DLB subjects</li> </ul>

AD—Alzheimer disease, DLB—dementia with Lewy bodies, ITT—intention to treat, MMSE—Mini-Mental State Examination, NPI—neuropsychiatric inventory, RCT—randomized controlled trial.

eight DLB patients given olanzapine, three subjects could not tolerate the drug, and only two patients appeared to benefit.<sup>54</sup> This series contrasted with the results of an RCT involving AD and DLB patients treated with olanzapine. Compared with placebo, DLB subjects receiving 5 to 10 mg of olanzapine had good response for psychotic features with no significant motor worsening and no hypersensitivity reactions.<sup>55</sup>

Antipsychotic agents should be used for patients with known or suspected DLB only after considering

risks and benefits. A trial of a cholinesterase inhibitor to treat neuropsychiatric symptoms should be considered before using a neuroleptic of any type (level II and III evidence).<sup>48</sup> Neuroleptics should be reserved for situations where the psychosis is causing serious distress or putting the patient or others at risk. It is difficult to make firm recommendations about agents, but atypical agents should probably be preferred over older agents. Initial doses should be low and should be titrated slowly while monitoring for functional decline (**Table 4**).

**Table 4. Medications relevant to DLB**

MEDICATIONS	COMMENTS
<b>CHOLINESTERASE INHIBITORS</b>	
<ul style="list-style-type: none"> <li>Rivastigmine (1.5 mg twice daily) increased every 2–4 wk to target 6–12 mg/d</li> <li>Donepezil (2.5 or 5 mg daily for 1 mo, then increase to 10 mg daily)</li> <li>Galantamine—no published case series or RCTs, (initial dose of 4 mg twice daily for 1 mo, then increase to 8 mg twice daily)</li> </ul>	<ul style="list-style-type: none"> <li>Most common side effect is nausea and vomiting; slow titration (especially with rivastigmine) could minimize this effect</li> <li>Contraindications include sick sinus syndrome and bradyarrhythmias, serious asthma or COPD, severe renal and liver failure</li> <li>Worsening of motor parkinsonism is a concern; DLB patients should be monitored</li> </ul>
<b>ANTI-PARKINSON'S MEDICATIONS</b>	
Levodopa-carbidopa combination (100/25 start 1/2 tablet daily; increase by 1/2 tablet increments to 1 tablet three times daily)	<ul style="list-style-type: none"> <li>Short-term side effects include nausea and hypotension</li> <li>Most relevant side effects to DLB are hallucinations, nightmares, and delirium</li> <li>Worsening of hallucinations and cognition not noted in small studies done</li> </ul>
<b>ATYPICAL NEUROLEPTICS</b>	
<ul style="list-style-type: none"> <li>Risperidone (0.25 mg twice daily with cautious titration to maximum dose of 1 mg twice daily)</li> <li>Olanzapine (2.5 mg titrated to 5–10 mg/d)</li> <li>Quetiapine (25 twice daily titrated to 150 mg/d)</li> </ul>	<ul style="list-style-type: none"> <li>Only risperidone is licensed in Canada to treat behavioural disturbance in dementia, but all atypical agents can cause neuroleptic sensitivity reactions</li> <li>Close monitoring of motor parkinsonism and cognition necessary for all agents</li> </ul>

*COPD—chronic obstructive pulmonary disease, DLB—dementia with Lewy bodies, RCT—randomized controlled trial.*

## Conclusion

Dementia with Lewy bodies is a common cause of dementia. It should be considered when patients with dementia have fluctuating attention and cognition, motor findings of parkinsonism, and hallucinations. A cholinesterase inhibitor should be considered for neuropsychiatric symptoms. Atypical neuroleptics should be used with caution and only when absolutely necessary due to a risk of serious sensitivity reactions. Levodopa-carbidopa combinations should be considered when motor symptoms cause problems. The role of family physicians in nonpharmacologic treatment is important, as with other dementias. 🍁

## Competing interests

None declared

**Correspondence to:** Dr Christopher Frank, Providence Continuing Care Centre, 340 Union St, PO Box 3600, Kingston, ON K7L 5A2; telephone (613) 548-7222, extension 2208; fax (613) 544-4017; e-mail frankc@pccchealth.org

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## CME

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### Dementia with Lewy bodies

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### Editor's key points

- Family physicians can diagnose dementia with Lewy bodies using clinical criteria including the presence of dementia with marked fluctuation in cognitive performance, visual hallucinations, and motor symptoms of parkinsonism.
- One randomized controlled trial and a few open-label studies suggest cholinesterase inhibitors, particularly rivastigmine, should be considered for neuropsychiatric symptoms.
- Case reports indicate levodopa-carbidopa combinations should be considered to control motor symptoms of parkinsonism.
- Patients with dementia with Lewy bodies risk rapid progression of parkinsonism if treated with neuroleptics. Small doses of atypical agents can be used to control psychotic symptoms as long as patients are monitored for functional decline.

### Points de repère du rédacteur

- Le diagnostic de démence à corps de Lewy est posé en présence d'une démence accompagnée de fluctuations de la performance cognitive, d'hallucinations visuelles et de symptômes moteurs de parkinsonisme.
- Un essai clinique randomisé et quelques études ouvertes suggèrent que les inhibiteurs de la cholinestérase, en particulier la rivastigmine, améliorent les symptômes neuropsychiatriques.
- L'utilisation de lévodopa/carbidopa pour contrôler les symptômes moteurs parkinsoniens est supportée par quelques études de cas.
- Les symptômes de parkinsonisme sont susceptibles de s'aggraver chez les patients ayant une démence à corps de Lewy traités avec des neuroleptiques. Les neuroleptiques atypiques peuvent être introduits à petites doses pour contrôler les symptômes psychotiques en surveillant les fonctions cognitives.

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